

## Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury

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### Abstract

**Background.** In critically ill patients with acute kidney injury, estimates of kidney function are used to modify drug dosing, adjust nutritional therapy and provide dialytic support. However, estimating glomerular filtration rate is challenging due to fluctuations in kidney function, creatinine production and fluid balance. We hypothesized that commonly used glomerular filtration rate prediction equations overestimate kidney function in patients with acute kidney injury and that improved estimates could be obtained by methods incorporating changes in creatinine generation and fluid balance.

**Methods.** We analysed data from a multicentre observational study of acute kidney injury in critically ill patients. We identified 12 non-dialysed, non-oliguric patients with consecutive increases in creatinine for at least 3 and up to 7 days who had measurements of urinary creatinine clearance. Glomerular filtration rate was estimated by Cockcroft–Gault, Modification of Diet in Renal Disease, Jelliffe equation and Jelliffe equation with creatinine adjusted for fluid balance (Modified Jelliffe) and compared to measured urinary creatinine clearance.

**Results.** Glomerular filtration rate estimated by Jelliffe and Modification of Diet in Renal Disease equation correlated best with urinary creatinine clearances. Estimated glomerular filtration rate by Cockcroft–Gault, Modification of Diet in Renal Disease and Jelliffe overestimated urinary creatinine clearance was 80%, 33%, 10%, respectively, and Modified Jelliffe underestimated GFR by 2%.

**Conclusion.** In patients with acute kidney injury, glomerular filtration rate estimating equations can be improved by incorporating data on creatinine generation and fluid balance. A better assessment of glomerular filtration rate in acute kidney injury could improve evaluation and management and guide interventions.

**Keywords:** acute kidney injury; Cockcroft–Gault; glomerular filtration rate; Jelliffe; modification of diet in renal disease

### Introduction

Acute kidney injury (AKI) is common among hospitalized patients, particularly critically ill patients, and is associated with increased morbidity and mortality [1–6]. Since a decline in kidney function contributes to the accumulation of many drugs [7–9], an accurate assessment of kidney function is required to optimize drug administration and other processes of care. However, estimating kidney function in AKI is challenging because commonly used equations are considered inaccurate and timed urine collections are cumbersome to perform [10]. Physicians and pharmacists sometimes use glomerular filtration rate (GFR) estimating equations developed for patients with chronic kidney disease (CKD) to ascertain levels of kidney function in AKI, such as Cockcroft–Gault or Modification of Diet in Renal Disease (MDRD). However, kidney function is not in steady state in AKI. Consequently, the Jelliffe equation was developed to estimate GFR in the setting of non-steady-state kidney function [10,11]. The relative performance of alternative GFR estimating equations in AKI has not been formally compared.

The Program to Improve Care in Renal Disease (PICARD) was a multi-centre cohort study examining patient characteristics and practice patterns associated with adverse and favourable outcomes after AKI [12]. Using data from PICARD, we hypothesized that GFR is relatively overestimated by the Cockcroft–Gault and MDRD equations compared to Jelliffe's equation and a Modified Jelliffe equation with serum creatinine concentration

**Table 1.** Baseline characteristics in patients for whom urine creatinine clearance was unavailable ( $n = 179$ ) and in patients for whom urine creatinine clearance was measured ( $n = 12$ )

	Patients without urine creatinine clearance ( $n = 179$ )	Patients with urine creatinine clearance ( $n = 12$ )	P-value
Mean age (years)	59.7 $\pm$ 16.9	59.3 $\pm$ 18.9	0.93
Gender (% male)	121/179 (67.6%)	4/12 (33.3%)	0.03
Race			0.16
Caucasian	153/179 (85.5%)	9/12 (75%)	
African American	13/179 (7.3%)	1/12 (8.3%)	
Hispanics	5/179 (2.8%)	2/12 (16.7%)	
Asian	5/179 (2.8%)		
Other	3/179 (1.6%)		
Mean baseline weight (kg) at hospital admission	81.9 $\pm$ 19.7	76.3 $\pm$ 15.1	0.33
Mean body surface area ( $m^2$ )	1.96 $\pm$ 0.24	1.90 $\pm$ 0.22	0.38
Diabetes (%)	52/179 (29.1%)	2/12 (16.7%)	0.36
Hypertension (%)	97/179 (54.2%)	6/12 (50%)	0.78
Chronic kidney disease (%)	56/179 (31.3%)	6/12 (50%)	0.20
APACHE III (at ICU admission)	60.7 $\pm$ 27.1	43.8 $\pm$ 26.1	0.06
Mean% fluid overload per body weight during study period	6.7 $\pm$ 9.0%	6.4 $\pm$ 10.4	0.92
Urine output during study period (median and IQR)	1512 (25%–75%; 99–2925)	1700 (25%–75%; 580–2820)	0.28
On diuretics (ever) (%)	165/179 (92.2%)	12/12 (100%)	0.61
Dialysed after study enrolment	109/179 (60.9%)	8/12 (66.7%)	0.47

Continuous variables are reported as mean  $\pm$  standard deviation.

Categorical variables are reported as percentage.

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit.

(sCr) adjusted for creatinine generation and fluid balance. Thus, we compared four alternative GFR estimating equations in a subset of the PICARD study population with measurements of urinary creatinine clearance.

## Subjects and methods

### Study participants

From February 1999 to August 2001, patients who underwent a nephrology consultation for AKI in the intensive care unit (ICU) of five different centres were evaluated by the PICARD study personnel for potential study participation. Informed consent was obtained from all study participants, and the protocol was in adherence with the Declaration of Helsinki. A complete description of PICARD data elements, data collection and management strategies has been previously detailed [12]. In PICARD, AKI was defined as an increase in sCr  $\geq 0.5$  mg/dL when the baseline sCr was  $<1.5$  mg/dL or an increase in sCr  $\geq 1.0$  mg/dL when the baseline creatinine was  $\geq 1.5$  mg/dL and  $<5.0$  mg/dL [12]. Baseline sCr was defined as the closest value within 6 months of hospital admission. Exclusion criteria included age  $<18$  years, prisoners, pregnant women, sCr  $> 5.0$  mg/dL, previous dialysis, kidney transplantation, AKI from urinary tract obstruction and hypovolaemia responsive to fluid. From the 618 patients included in the database, we selected all non-oliguric patients with a consecutive increase in sCr over 3–7 days prior to any dialysis ( $n = 191$ ). Among the 191 patients, 12 had measurements of urinary creatinine clearance. sCr concentrations were generally measured every 24 h. We included the first creatinine value every morning in the analyses. Laboratory studies and fluid status were obtained daily throughout the ICU stay. The patients who were dialysed after the 3- to 7-day period were not excluded, since sCr and fluid balance included in this analysis were not affected by subsequent renal replacement therapy.

### Estimation of GFR using Cockcroft–Gault, MDRD, Jelliffe and Modified Jelliffe equations

We estimated GFR (mL/min) using the well-known equation described by Cockcroft–Gault [13], which includes the following variables: age, gender, weight and sCr. We estimated GFR (mL/min/1.73 m<sup>2</sup>) using the abbreviated MDRD equation (age, race, gender and sCr) as previously defined [14]. To allow comparisons, we also computed the Cockcroft–Gault estimates indexed to 1.73 m<sup>2</sup> body surface area (BSA).

We computed the Jelliffe equation for unstable kidney function [10]. This equation has been previously validated in patients with non-steady-state kidney function [10,11]. In summary, the volume of distribution is multiplied by the difference between the sCr measured on the first day (initial creatinine) and the second day and creatinine production is added to this product. The whole sum is multiplied by 100, divided by 1440 and again divided by the average sCr. The equation can be summarized as follows:

$$\begin{aligned} & ((\text{Volume of distribution} \times (\text{sCr on day1} - \text{sCr on day2})) \\ & + \text{creatinine production}) \times 100/1440/\text{average sCr}. \end{aligned}$$

This simplified equation is accurate for sCr measured every 24 h. When sCr rises, sCr on Day 2 is used instead of average sCr.

The volume of distribution in deciliters is estimated to be equal to  $0.4 \times \text{weight (kg)} \times 10$ . Body weight is defined as initial hospital admission weight.

Creatinine production (mg/day) is computed using the following equation:  $[29.305 - (0.203 \times \text{age})] \times \text{weight} \times [1.037 - (0.0338 \times \text{average Cr})] \times \text{correction for gender (0.85 for males and 0.765 for females)}$ .

Since this equation takes into account sCr fluctuations and creatinine production over time, but not fluid balance variations, which can also significantly influence serum creatinine measurements [15], we adjusted every sCr according to the cumulative daily fluid balance using the following equation [15]:

$$\text{Adjusted creatinine} = \text{sCr} \times \text{correction factor}$$

$$\begin{aligned} \text{Correction factor} = & [\text{hospital admission weight (kg)} \\ & \times 0.6 + \Sigma (\text{daily fluid balance})]/\text{hospital admission weight} \times 0.6. \end{aligned}$$

The adjusted sCr was substituted for the measured sCr in the Jelliffe equation to compute the Modified Jelliffe GFR. Jelliffe and Modified Jelliffe equations were indexed to 1.73 m<sup>2</sup> body surface area.

We computed urinary creatinine clearance using the following equation [16]:

$$\begin{aligned} \text{urinary creatinine clearance (mL/min)} = & \text{urine creatinine (mg/dl)} \\ & * \text{urine volume (mL)}/\text{creatinine (mg/dl)} * \text{time (min)}. \end{aligned}$$

Urinary creatinine clearance data were computed with and without indexing to body surface area.

For Table 1, we calculated the percentage of fluid overload per body weight using the following equation [17]:

$$\{\Sigma \text{daily [fluid intake (L) - total output (L)]}/\text{body weight (kg)}\} \times 100.$$

**Table 2.** Urine creatinine clearance versus creatinine clearance estimated by Cockcroft–Gault, MDRD, Jelliffe and Modified Jelliffe equations in 12 patients

Creatinine used for calculation	First day	Mean	Second day
Serum creatinine (mg/dL)	3.6 ± 1.5	3.8 ± 1.6	4.0 ± 1.7
Cockcroft–Gault (mL/min)	24.9 ± 12.8	23.7 ± 12.4*	22.5 ± 12.1
Cockcroft–Gault (mL/min/1.73 m <sup>2</sup> )	22.5 ± 10.9	21.4 ± 10.6	20.3 ± 10.3
MDRD (mL/min/1.73 m <sup>2</sup> )	18.3 ± 7.3	17.3 ± 7.2*	16.3 ± 7.1
Jelliffe (mL/min/1.73 m <sup>2</sup> )		15.7 ± 10.0	
Modified Jelliffe (mL/min/1.73 m <sup>2</sup> )		14.4 ± 9.3	
Urine creatinine clearance (mL/min)	16.1 ± 7.1	15.4 ± 7.1	14.8 ± 7.1
Urine creatinine clearance adjusted for BSA (mL/min/1.73 m <sup>2</sup> )	14.6 ± 6.1	14.0 ± 6.1	13.4 ± 6.1

\*We reported the mean of the two glomerular filtration rate (GFR)s for Cockcroft–Gault and MDRD. When using the mean creatinine of the first day and second day, instead of the mean of the two GFRs, the results were very similar (for Cockcroft–Gault: 23.6 ± 12.4 mL/min when using the mean creatinine versus 23.7 ± 12.4 mL/min when using the mean GFR and for MDRD, 17.2 ± 7.2 mL/min/1.73 m<sup>2</sup> when using the mean creatinine versus 17.3 ± 7.2 mL/min/1.73 m<sup>2</sup> when using the mean GFR).

MDRD, Modification of Diet in Renal Disease; BSA, body surface area.

### Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median and interquartile range and compared using the Student *t*-test or the Wilcoxon rank-sum test, as appropriate. Categorical variables were expressed as proportions and compared with the chi-square or Fisher Exact test, as appropriate. Correlation coefficients among the four equations with urinary creatinine clearance were computed with the Spearman correlation coefficient as appropriate. We used Bland–Altman plots to evaluate the performance of alternative equations as a predictor of urinary creatinine clearance. All statistical tests were two-sided, and *P* < 0.05 was considered significant. Statistical analyses were conducted using SPSS 15.0 (Chicago, IL, USA), NCSS 2007 (Kaysville, UT, USA) and GraphPad Prism, version 5.0 (San Diego, CA, USA).

## Results

We identified 191 non-oliguric patients with consecutive increases in sCr over 3–7 days prior to any dialysis. Out of the 191 patients, 12 had measurements of urinary creatinine clearance. The duration of collections ranged from 4 to 24 h. Four of the 12 patients received diuretics during urinary creatinine clearance measurement, the doses being 40, 80, 240 and 780 mg/day. The baseline demographic, clinical and laboratory variables in patients with and without measurements of urinary creatinine clearance are shown in Table 1. The mean daily cumulative fluid balance ranged from 2.0 ± 3.6 L/day to 6.7 ± 7.1 L/day over the 7-day period.

Urinary creatinine clearance was measured in 12 patients and compared with estimated GFRs (Table 2 and Figure 1A–D). The correlations among urinary creatinine clearance and Cockcroft–Gault, MDRD, Jelliffe and Modified Jelliffe were 0.67 (*P* = 0.009), 0.89 (*P* < 0.001), 0.75 (*P* = 0.002) and 0.72 (*P* = 0.003), respectively. The mean percentages of overestimation of Cockcroft–Gault, MDRD and Jelliffe compared to urinary creatinine clearances were 80%, 33%, 10%, respectively. Modified Jelliffe underestimated GFR by 2%.

The mean sCr ranged between 3.6 ± 1.5 and 4.0 ± 1.7 mg/dL when urinary creatinine clearances were measured. To assess values of the GFR estimating equations in a larger cohort, we computed the four equations (Cockcroft–Gault, MDRD, Jelliffe and Modified Jelliffe) in all

non-oliguric patients with a consecutive increase in sCr over 3–7 days prior to any dialysis (*n* = 191). Overall, the mean sCr ranged from 2.3 to 4.6 mg/dL over 7 days. Values of estimated GFR using the Cockcroft–Gault and MDRD equations were significantly higher than those obtained from the Jelliffe equations (Figure 2). Cockcroft–Gault estimates were 49% and 69% higher than the Jelliffe and Modified Jelliffe equations, respectively (29% and 47% when Cockcroft–Gault was adjusted for BSA). MDRD estimates were 15% and 30% higher than the Jelliffe and Modified Jelliffe equations, respectively. The mean absolute difference between Cockcroft–Gault and Modified Jelliffe was 12.1 mL/min (range 8.9–16.3 mL/min) and between MDRD GFR and Modified Jelliffe was 5.4 mL/min (range 3.4–7.5 mL/min).

As shown in Figure 2, the relative overestimation in Cockcroft–Gault GFR compared to Modified Jelliffe GFR estimates was higher at AKI diagnosis (16.3 mL/min) and decreased as kidney function declined over time (8.9 mL/min). Additionally, the relative overestimation was larger for patients with lower initial sCr.

## Discussion

Equations used to estimate GFR in CKD such as the Cockcroft–Gault and MDRD equations are often applied in the acute hospital setting by physicians and pharmacists, despite the absence of evidence from prospective studies supporting the validity or safety of that approach. In fact, few studies have attempted to improve estimation of GFR in critically ill patients and these studies included subjects with stable kidney function in various settings. [18–21]

In AKI, three main factors influence the estimation of kidney function, namely true kidney function, fluctuations in creatinine production and fluid balance [15]. In 2002, Jelliffe published an equation to estimate GFR in patients with unstable (non-steady state) kidney function that considered fluctuations in kidney function and creatinine production without requiring timed urine collection [10]. The Jelliffe equation is based on the concept that daily changes in sCr depend on the difference between creatinine production

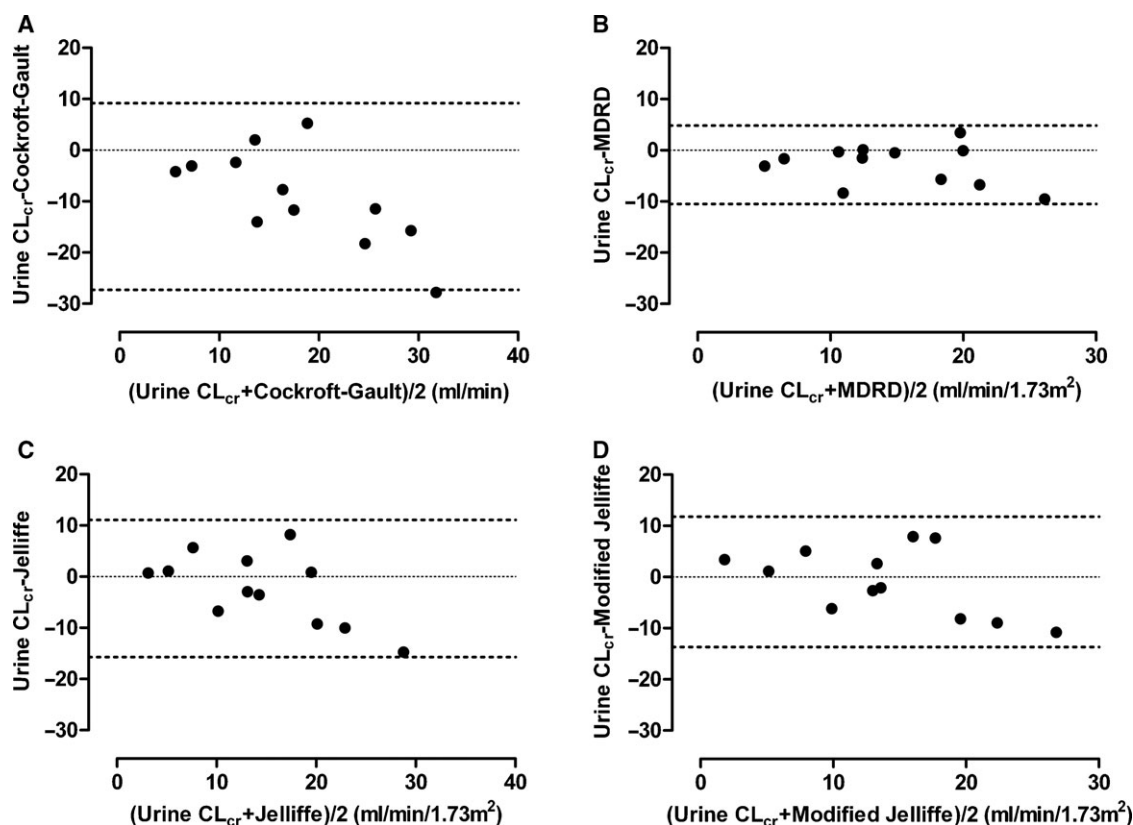


Fig. 1. Bland–Altman method between urine creatinine clearance and glomerular filtration rate estimated by the Cockcroft–Gault (A; mL/min), MDRD (B; mL/min/1.73 m<sup>2</sup>), Jelliffe (C; mL/min/1.73 m<sup>2</sup>) and Modified Jelliffe (D; mL/min/1.73 m<sup>2</sup>) equations.

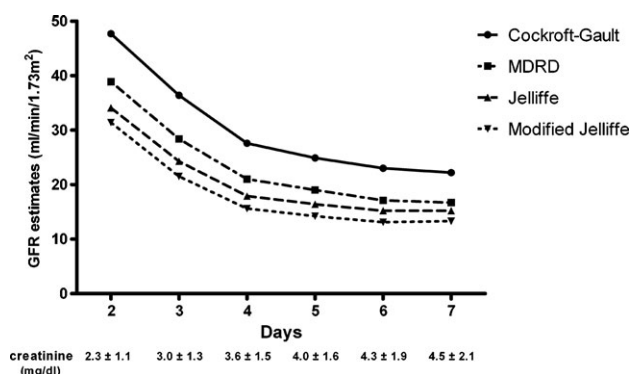


Fig. 2. GFR estimates by Cockcroft–Gault\*, MDRD, Jelliffe and Modified Jelliffe equations.

and excretion [10,11]. Creatinine production is adjusted for age and also for CKD, as creatinine production generally decreases with declining kidney function. The Jelliffe equation was validated against 584 urinary creatinine clearances from 29 patients [10]. The results obtained from the equation were close to those from classical measurements of 24-h urinary creatinine clearance [11].

To estimate total body water, Jelliffe used a volume of distribution of creatinine (in litres) equivalent to 0.4 [11,22] (instead of 0.6) × body weight (kilograms), as is used currently [23]. We performed our correction for fluid balance

using 0.4 and 0.6 and obtained similar results with both coefficients (data not shown). The Jelliffe equation did not include variations in sCr due to fluid administration [10,15]. Creatinine is a hydrosoluble substance and its concentration changes with fluctuations in total body water [24]. Aggressive fluid resuscitation can lower sCr and falsely increase estimated GFR [25]. Critically ill patients frequently experience large positive fluid balances. In a previous multicentre study, the mean daily fluid balance was 0.60 ± 1.50 L and 0.39 ± 1.21 L in patients requiring and not requiring renal replacement therapy, respectively [26].

The relative overestimation of GFR in AKI with both Cockcroft–Gault and MDRD was more prominent when baseline GFR was higher. Small absolute changes in sCr will be reflected as large relative changes in GFR with a lower sCr. In our study, patients had a mean positive fluid balance of 0.95 L/day. Patients with fluid accumulation would have GFR overestimated the most by the Cockcroft–Gault and MDRD equations. Therefore, in practice, it is arguably more important to adjust GFR for creatinine production and fluid balance at the beginning of an AKI episode, when the initial sCr is within the normal range, or nearly so.

It is important to highlight the magnitude of variation among these available methods since GFR estimation in AKI could be used to adjust drug dosing and could also influence the timing of initiation of renal replacement therapy. A better assessment of GFR in AKI could be used to

improve the evaluation of AKI and concomitant therapeutic interventions. In critically ill patients in whom precise adjustment of drugs is essential, these differences would have a direct clinical consequence in a short period of time. For instance, underdosing or overdosing an antibiotic in this setting is likely to have serious repercussions. The Cockcroft–Gault equation is most commonly used to estimate GFR for drug dosing in CKD, yet is known to overestimate kidney function in AKI. Moreover, it is generally not adjusted for BSA, which may further contribute to the overestimation of GFR. The use of the Jelliffe equations could help avoid this pitfall in the setting of AKI, if the Jelliffe equations provide more accurate estimates of GFR. In addition, the Jelliffe and Modified Jelliffe equations could be easily integrated in a computer program to facilitate dosage regimens of drugs that have a narrow therapeutic index. Other drugs, including fluconazole, extended spectrum penicillins, cephalosporins and quinolones, with wider therapeutic indices could be prescribed more safely and at potentially lower expense when guided by better GFR estimating equations applicable to the hospital setting in the context of AKI. Moreover, the Modified Jelliffe equation can still be applied to patients with concomitant CKD, or those later in the course of AKI. While the absolute difference in GFR appears to be relatively small, these equations could be used to assess time points to initiate dialysis in non-oliguric patients. No previous study on dialysis modality or dosage has taken into account the influence of residual kidney function on outcomes [27–36]; therefore, these equations could better characterize and compare kidney function in these patients.

This study has several strengths. The PICARD study was a prospective multicentre study with longitudinal clinical and laboratory data and daily information on fluid administration, loss and balance. The population is reasonably representative of critically ill patients with AKI. Our study also has several limitations. We did not use a ‘gold standard’ method to assess GFR. Timed urine collections have not been thoroughly validated as a proxy for kidney function in AKI [10,11]. Comparisons of the estimated GFR with measured urinary creatinine clearance were limited due to the small sample size and the advanced stage of AKI in these patients (mean sCr levels ranged from 3.6 to 4.0 mg/dL). Despite these limitations, Cockcroft–Gault and MDRD equations relatively overestimated creatinine clearance in AKI compared to the Jelliffe equations. These findings are in sharp contrast to results observed in steady state, where the MDRD equation has been shown to underestimate GFR by as much as 20 mL/min/1.73 m<sup>2</sup> or more, especially in persons with normal or near normal kidney function [37]. The Bland–Altman plots revealed a smaller deviation for the MDRD equation compared to the Jelliffe; however, this may reflect the factors included in Jelliffe, such as the generation of creatinine which requires consideration of two sequential values of serum creatinine. Since AKI is a non-steady state condition, we anticipate that the two creatinine values would be different based on the catabolic rate and hence result in a greater variation in the estimated clearance, whereas the MDRD equation inherently focuses on a single sCr alone. In patients with less severe AKI, there is considerable variation in the estimated GFR when using the Cockcroft–Gault, MDRD, Jelliffe and

Modified Jelliffe equations and we could not validate our results with urine creatinine clearance in all patients. Future studies in which more precise measures of kidney function are obtained in larger populations can help to refine the Jelliffe equation and its correction factor for fluid balance. Since anuric and oliguric patients have very low creatinine clearances, study results should not be generalized to these patients. Finally, additional studies are required to better estimate GFR during recovery of kidney function, when similar issues of non-steady state conditions are at play.

In conclusion, among critically ill patients with severe AKI, the traditional GFR estimating equations tend to relatively overestimate kidney function and the Cockcroft–Gault equation should not be applied. These results should be further validated using a larger sample of patients and emphasize the need to further enhance techniques to estimate GFR during evolution of, and recovery from, AKI.

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## Outcome definitions in non-dialysis intervention and prevention trials in acute kidney injury (AKI)

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### Abstract

**Background.** The risk, injury, failure, loss-of-function, end-stage-renal-failure (RIFLE) and acute kidney injury network (AKIN) consensus definitions of acute kidney

injury (AKI) were established in part to facilitate comparison of trials. Contrast-induced nephropathy (CIN) has traditionally used a less demanding definition.